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FAEGRE & BENSON LLP
PATENT DOCKETING
2200 WELLS FARGO CENTER
90 SOUTH SEVENTH STREET
MINNEAPOLIS, MN 55402-3901

EXAMINER	
BLANCHARD, DAVID J	

ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 12/01/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/714,391	GRIFFITHS ET AL.	
	Examiner	Art Unit	
	David J. Blanchard	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 September 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-43* is/are pending in the application.

4a) Of the above claim(s) *4,33 and 36-41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3, 5-32, 34-35 and 42-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/30/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-43 are pending

Claims 1, 8, 23 and 30 have been amended.

Claims 42-43 have been added.

2. Claims 4, 33 and 36-41 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

3. Claims 1-3, 5-32, 34-35 and 42-43 are under examination to the extent that the tumor-associated antigen is EGP-1.

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

5. This Office Action contains New Grounds of Rejections.

Information Disclosure Statement

6. The information disclosure statement (IDS) submitted on 30 October 2006 has been fully considered by the examiner and a signed copy of the IDS is attached with this Office Action. Applicant is advised that citation no. 2 on the IDS filed 30 October 2006 is a duplicate citation of a reference previously considered by the examiner (see PTO-892 mailed 6/2/2006). Thus, citation no. 2 on the IDS filed 30 October 2006 has been crossed out on the present IDS to avoid delays at the time of allowance.

Withdrawn Objections/Rejections

7. The objection to the specification as not containing the updated status of USSN 09/337,756 at pp. 7 and 11 of the specification is withdrawn in view of the amendment to the specification filed 9/1/2006.

8. The objection to claims 1 and 8 as being drawn to non-elected inventions is withdrawn in view of the amendments to the claims.

9. The objection to claim 23 in the recitation "with an dissociation constant..." is withdrawn in view of the amendment to the claim.

10. The rejection of claim 30 under 35 U.S.C. 112, second paragraph as being indefinite in the recitation of the trademark TAXOL® is withdrawn in view of the amendment to the claim.

11. The rejection of claims 1-3, 5, 9-13, 15-16, 24-32, 34-35 under 35 U.S.C. 102(b) as being anticipated by Hansen et al [a] (WO 99/66951, 12/29/1999) is withdrawn in view of the amendments to the claims.

12. The provisional rejection of claims 1-3, 5, 9-13, 15-16, 24-32, 34-35 under 35 U.S.C. 102(e) as being anticipated by copending Application No. 09/337,756 is withdrawn in view of the amendments to the claims.

13. The rejection of claims 7-8 under 35 U.S.C. 103(a) as being unpatentable over Hansen et al [a] (WO 99/66951, 12/29/1999) in view of Basu et al (International Journal of Cancer, 62:472-479, 1995) is withdrawn in view of the amendments to the claims.

14. The rejection of claims 6, 10, 14 and 23 under 35 U.S.C. 103(a) as being unpatentable over Hansen et al [a] (WO 99/66951, 12/29/1999) in view of Barbet et al (U.S. Patent 5,256,395, issued 10/26/1993) and Haisma et al (Blood, 92(1):184-190, 1998) is withdrawn in view of the amendments to the claims.

15. The rejection of claims 17-22 under 35 U.S.C. 103(a) as being unpatentable over Hansen et al [a] (WO 99/66951, 12/29/1999) in view of Danks et al (Clinical Cancer research 5:917-924, April 1999) and Searle et al (WO 00/43541, published 7/27/2000) is withdrawn in view of the amendments to the claims.

16. The rejection of claims 1-3, 5-32 and 34-35 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 16 and 18 of U.S. Patent No. 6,962,702 B2 in view of Hansen et al [a] (WO 99/66951, 12/29/1999) and Basu et al (International Journal of Cancer, 62:472-479, 1995) and Barbet et al (U.S. Patent 5,256,395, issued 10/26/1993) and Haisma et al (Blood, 92(1):184-190, 1998) and Danks et al (Clinical Cancer research 5:917-924, April 1999) and Searle (WO 00/43541, published 7/27/2000) is withdrawn in view of the amendments to the claims.

17. The provisional rejection of claims 1-3, 5-32 and 34-35 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 12-18 of copending Application No. 09/337,756 (now allowed) in view of in view of

Hansen et al [a] (WO 99/66951, 12/29/1999) and Basu et al (International Journal of Cancer, 62:472-479, 1995) and Barbet et al (U.S. Patent 5,256,395, issued 10/26/1993) and Haisma et al (Blood, 92(1):184-190, 1998) and Danks et al (Clinical Cancer research 5:917-924, April 1999) and Searle (WO 00/43541, published 7/27/2000) is withdrawn in view of the amendments to the claims.

Objections Maintained

18. The objection to the specification as not containing the updated status of USSN 10/116,116 at pp. 7 and 11 of the specification is maintained.

The examiner acknowledges that USSN 10/116,116 is presently copending, however, should the status of USSN 10/116,116 change during the pendency of the present application, applicant should update the status accordingly, i.e., "now abandoned", "now US Patent...". Thus, this objection will be maintained until the present claims are in condition for allowance or until the status of copending USSN 10/116,116 changes, whichever is earlier.

New Grounds of Objections/Rejections

19. Claims 1 and 42 are objected to for the following informalities:

a. Claim 1 is objected to in the recitation "are in ratios of from 5:1 to 1:5", which is grammatically incorrect. Consider revising the claim to recite "are in a ratio from 5:1 to 1:5.

b. Claim 42 is objected to in the recitation "ratio is of from 2:1 to 1:2", which is grammatically incorrect. Consider revising the claim to recite "ratio is from 2:1 to 1:2.

Appropriate correction is required.

20. Claims 1-3, 5-32, 34-35 and 42-43 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The response filed 9/1/2006 has introduced NEW MATTER into the claims. As presently amended claim 1 recites that the multispecific targeting protein and the hapten-enzyme covalent conjugate of the non-covalently bound complex in the claimed method are in ratios of from 5:1 to 1:5, or the ratio is from 2:1 to 1:2, or the ratio is 2:1 (newly added claims 42-43). Applicant points to paragraph [0027] and Tables 1-6 as filed for support of presently amended claim 1 and newly added claims 42-43. This has been fully considered but is not found persuasive. The as-filed disclosure as pointed to by applicant appears to provide adequate written support for the limitation wherein the bispecific antibody and the hapten-enzyme covalent conjugate of the non-covalently bound complex are mixed prior to administration (i.e., "pre-mixed") in a ratio from 5:1 to 1:5, or in a ratio from 2:1 to 1:2, or is 2:1, however, the claims recite that the multispecific targeting protein and the hapten-enzyme covalent conjugate are in ratios of from 5:1 to 1:5, or of from 2:1 to 1:2, or is 2:1, rather than mixed in said ratios prior to administration. The claims do not recite that the multispecific targeting protein is a bispecific antibody and wherein the bispecific antibody and the hapten-enzyme covalent conjugate of the non-covalently bound complex are mixed prior to administration in a ratio from 5:1 to 1:5, or a ratio from 2:1 to 1:2, or in a ratio 2:1. Further, the as-filed disclosure pointed to by applicant only discloses the presently claimed ratios in the context of a bispecific antibody and a hapten-enzyme covalent conjugate and not the broader genus of "multispecific targeting protein". As presently amended the claims now recite limitations, which were not clearly disclosed in the specification as-filed, and now change the scope of the instant disclosure as filed. Such limitations recited in presently amended claim 1 and newly added claims 42-43, which did not appear in the specification, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C 112. Applicant is required to provide sufficient written support for the limitations recited in presently amended claim 1 and newly added claims 42-43in the specification or claims, as-filed, or remove these limitations from the claims in response to this Office Action.

21. Claims 1-3, 5, 7-13, 15-16, 24-32, 34-35 and 42-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hansen et al [a] (WO 99/66951, 12/29/1999, cited on PTO-892 mailed 6/2/2006) in view of Gautherot et al (The Journal of Nuclear Medicine, 39(11):1937-1943, November 1998) and Basu et al (International Journal of Cancer, 62:472-479, 1995, cited on PTO-892 mailed 6/2/2006).

The claims are being interpreted as drawn to a method of treating EGP-1 expressing tumor cells in a human comprising administering in sequence a non-covalently bound complex to said subject thereby forming a EGP-1 localized complex, wherein said non-covalently bound complex comprises a multispecific targeting protein comprising at least one EGP-1-binding site and at least one hapten-binding site, and a hapten-enzyme covalent conjugate, optionally administering a clearing agent that is an anti-idiotypic antibody to the multispecific targeting protein, or a galactosylated anti-idiotypic antibody to the multispecific targeting protein, and administering a chemotherapeutic drug or prodrug (i.e., CPT-11), capable of being converted to a more active drug by the EGP-1 localized complex, wherein the multispecific targeting protein and the hapten-enzyme conjugate are mixed prior to administration in a ratio from 5:1 to 1:5, or is from 2:1 to 1:2, or the ratio is 2:1 and wherein the chemotherapeutic prodrug has greater solubility than the active drug produced by the non-covalently bound complex and the prodrug is a prodrug of a camptothecin, doxorubicin, taxol, actinomycin, maytansine, calicheamicin or epithilone class of drug, is a prodrug of SN-38 or is the prodrug CPT-11. Further, the multispecific targeting protein is a mutlispecific antibody or multispecific antibody fragment and is at least bispecific, is multivalent, murine, chimeric, humanized or human and the hapten-enzyme comprises at least one hapten, selected from HSG, DTPA, indium-DTPA, DOTA, indium-DOTA, yttrium-DOTA, fluorescein or biotin and the haptens are linked by a peptide from 2-10, 2-5 or 3 amino acid residues in length and the enzyme of the hapten-enzyme conjugate is an esterase, amidase, glucuronidase, galactosidase or carboxylesterase.

Hansen et al [a] teach a method of treating a patient comprising administering a bispecific antibody or fragment having at least one arm that binds a targeted tissue or a tumor-associated antigen and at least one other arm that binds a hapten and a hapten-

enzyme covalent conjugate comprising at least one hapten, wherein the hapten-enzyme conjugate is mixed with the targeting bispecific antibody prior to administration (i.e., non-covalently bound complex), optionally administering a galactosylated anti-idiotypic antibody (clearing agent) to the bispecific antibody of the non-covalent complex to clear non-localized non-covalent complexes and administering a chemotherapeutic drug or prodrug that is converted to a more active drug by the pre-targeted enzyme (i.e., target-tissue-localized complex) (see entire document, particularly pp. 4-5, 9-11, 28, lines 20-25, pg. 29, lines 18-21, pg. 36, Examples 13-14 and 26). Hansen et al [a] also teach bi-specific or multispecific antibodies and antigen-binding fragments thereof that are monovalent or divalent (pg. 19, lines 14-20), are murine, chimeric, humanized or human antibodies and the hapten-enzyme comprises at least one hapten selected from fluorescein, DTPA, indium-DTPA, NOTA, DOTA, indium-DOTA and yttrium-DOTA wherein the haptens are linked by a peptide from 2-10 amino acid residues and the enzyme is a glucuronidase or a carboxylesterase, and "can be adopted for use with any enzyme-drug pair" (pg. 30, lines 29-30) according to Hansen et al [a] (see pg. 11-16, 19, 23-24, 29-31, 33-34). Further, Hansen et al [a] teach various prodrugs including epirubicin, topotecan, maytansinoids, calicheamicins and CPT-11, which is converted by carboxylesterase to the active drug SN-38 that remains in the vicinity of the tumor due to its poor solubility, i.e., the prodrug has a greater aqueous solubility than the active drug produced by the non-covalent complex (see pp. 28-30, 33-34). Hansen et al [a] do not specifically teach wherein the bispecific antibody binds EGP-1 or wherein the bispecific antibody and the hapten-enzyme conjugate are mixed prior to administration in a ratio from 5:1 to 1:5, or 2:1 to 1:2, or the ratio is 2:1. These deficiencies are made up for in the teachings of Gautherot et al and Basu et al.

Gautherot et al teach bispecific antibody-targeted bivalent haptens wherein saturation of the bispecific antibody occurred at a 2:1 ratio of bispecific antibody to bivalent hapten (i.e., 1 mol to 0.5 mol) (see entire document, particularly abstract, pg. 1939, 2nd col., pg. 1942 and Fig. 3).

Basu et al teach the epithelial glycoprotein-1 (EGP-1) expressed in various human tumors of epithelial origin including breast, bladder, lung, ovary, prostate,

pancreas and stomach and a monoclonal antibody to the EGP-1 antigen, which targets several carcinoma types in patients (see entire document, particularly pg. 472).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced method of treating EGP-1 expressing tumor cells in human patients comprising administering in sequence (i) a non-covalently bound complex comprising a bispecific antibody comprising at least one EGP-1-binding site and at least one hapten-binding site, and a hapten-enzyme covalent conjugate wherein the bispecific antibody and hapten-enzyme conjugate are mixed prior to administration in a ratio of 2:1, (ii) optionally administering a clearing agent that is an anti-idiotypic antibody to the bispecific antibody, and (iii) administering a chemotherapeutic drug or prodrug, capable of being converted to a more active drug by the EGP-1 localized complex for therapeutic benefit in human tumor patients.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to have produced method of treating EGP-1 expressing tumor cells in human patients comprising administering in sequence (i) a non-covalently bound complex comprising a bispecific antibody comprising at least one EGP-1-binding site and at least one hapten-binding site, and a hapten-enzyme covalent conjugate wherein the bispecific antibody and hapten-enzyme conjugate are mixed prior to administration in a ratio of 2:1, (ii) optionally administering a clearing agent that is an anti-idiotypic antibody or a galactosylated anti-idiotypic antibody to the bispecific antibody, and (iii) administering a chemotherapeutic drug or prodrug, capable of being converted to a more active drug by the EGP-1 localized complex for therapeutic benefit in human tumor patients in view of Hansen et al [a] and Gautherot et al and Basu et al because Hansen et al [a] teach a method of treating a patient comprising administering a bi-specific antibody or fragment thereof comprising at least one arm that binds a tumor-associated antigen and at least one other arm that binds a hapten and a hapten-enzyme covalent conjugate comprising at least one hapten, wherein the hapten-enzyme conjugate is mixed with the targeting bi-specific antibody prior to administration (i.e., non-covalently bound complex), optionally administering an anti-idiotypic antibody or a galactosylated anti-idiotypic

antibody (i.e., clearing agent) to said bispecific antibody to clear unbound non-covalent complexes and administering a chemotherapeutic prodrug that is converted to a more active drug by the pre-targeted enzyme and Gautherot et al teach bispecific antibody-targeted bivalent haptens wherein saturation of the bispecific antibody occurred at a 2:1 ratio of bispecific antibody to bivalent hapten (i.e., 1 mol to 0.5 mol) and Basu et al teach the EGP-1 antigen expressed in various human tumors of epithelial origin including breast, bladder, lung, ovary, prostate, pancreas and stomach as well as a monoclonal antibody to the EGP-1 antigen. Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to optimize the pre-targeting method of Hansen et al [a] by mixing the bispecific antibody and hapten-enzyme conjugate prior to administration in a ratio of 2:1 to saturate the bispecific antibody and target the human pancarcinoma antigen, EGP-1, for therapeutic benefit in a variety of human tumor patients, and the targetable conjugate (i.e., hapten-enzyme) of Hansen et al [a] provides flexibility in the therapeutic agent without the need for raising new bi-specific antibodies (see pg. 3, lines 18-25). Thus, there would be an advantage to using the method of Hansen et al [a] in targeting the EGP-1 antigen that is expressed in numerous human tumors, including breast, bladder, lung, ovary, prostate, pancreas and stomach and one of ordinary skill in the art would have a reasonable expectation of success in view of the teachings of Basu et al providing evidence that an EGP-1 antibody targets several carcinoma types in patients. Thus, it would have been *prima facie* obvious to one skilled in the art at the time the invention was made to have produced method of treating EGP-1 expressing tumor cells in human patients comprising administering in sequence (i) a non-covalently bound complex comprising a bispecific antibody comprising at least one EGP-1-binding site and at least one hapten-binding site, and a hapten-enzyme covalent conjugate wherein the bispecific antibody and hapten-enzyme conjugate are mixed prior to administration in a ratio of 2:1, (ii) optionally administering a clearing agent that is an anti-idiotypic antibody to the bispecific antibody, and (iii) administering a chemotherapeutic drug or prodrug, capable of being converted to a more active drug by the EGP-1 localized complex for

therapeutic benefit in human tumor patients in view of Hansen et al [a] and Gautherot et al and Basu et al.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

22. Claims 1-3, 5-7, 9-16, 23-32, 34-35 and 42-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hansen et al [a] (WO 99/66951, 12/29/1999) in view of Gautherot et al (The Journal of Nuclear Medicine, 39(11):1937-1943, November 1998) and Barbet et al (U.S. Patent 5,256,395, issued 10/26/1993, cited on PTO-892 mailed 6/2/2006) and Haisma et al (Blood, 92(1):184-190, 1998, cited on PTO-892 mailed 6/2/2006).

Claims 1-3, 5, 7, 9, 11-13, 15-16, 24-32, 34-35 and 42-43 and their interpretation have been described supra.

Claims 6, 10, 14 and 23 are being interpreted as being drawn to a method of treating target cells in a subject comprising administering in sequence a non-covalently bound complex to said human patient thereby forming a target-tissue localized complex, wherein said non-covalently bound complex comprises a multispecific targeting protein comprising at least one target-binding site and one hapten-binding site (i.e., HSG), and a hapten-enzyme covalent conjugate, optionally administering a clearing agent, and administering a chemotherapeutic drug or prodrug, capable of being converted to a more active drug by the target-tissue localized complex, and wherein the multispecific targeting protein and the hapten-enzyme conjugate are mixed prior to administration in a ratio from 5:1 to 1:5 and wherein the non-covalently bound complex is injected intravenously, and the haptens are attached via a single reaction site to the enzyme and the multispecific targeting protein binds to both its antigen target and to its hapten target with a dissociation constant of at least 10^{-7}, more preferably at least 10^{-9}.

Hansen et al [a] has been described supra. Hansen et al [a] do not specifically teach wherein the bispecific antibody and the hapten-enzyme conjugate are mixed prior to administration in a ratio from 5:1 to 1:5 or wherein the non-covalently bound complex is injected intravenously, the haptens (i.e., HSG) are attached via a single reaction site

to the enzyme and the bispecific antibody binds to both its antigen target and to its hapten target with a dissociation constant of at least 10^{-7}, more preferably at least 10^{-9}. These deficiencies are made up for in the teachings of Gautherot et al and Barbet et al and Haisma et al.

Gautherot et al have been described supra.

Barbet et al teach multivalent, multispecific antibodies or antigen-binding fragments thereof comprising two or more binding sites, wherein at least one binding site has affinity towards a hapten moiety (i.e., HSG) and at least one binding site has high affinity towards a tumor-associated antigen and a carrier molecule (affinity enhancement probe) comprising a therapeutic agent and at least two hapten moieties wherein the tumor-associated antigen binding site has a dissociation constant smaller than 10^{-8}M and the hapten binding site has a dissociation constant between 10^{-9}-10^{-7} and is administered by intravenous injection (see entire document, particularly Figures 1-3 and columns 2, 4-5, 6, lines 1-24, col. 8, lines 51-52).

Haisma et al teach that chemical conjugation of enzymes in antibody-directed enzyme prodrug therapy results in conjugate heterogeneity due to the lack of specificity of the reagents used for conjugation and necessitates additional purification steps and often results in reduced enzymatic activity or diminished binding activity of the conjugate, whereas recombinantly produced conjugates consist of a uniform product with predictable properties (see entire document, particularly, pg. 184, 2nd col. and pg. 188, 2nd col.).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced method of treating tumor cells in a patient comprising administering in sequence (i) a non-covalently bound complex comprising a bispecific antibody comprising at least one tumor-binding site and one hapten-binding site, and a hapten-enzyme covalent conjugate wherein the bispecific antibody and hapten-enzyme conjugate are mixed prior to administration in a ratio of 2:1, (ii) optionally administering a clearing agent that is an anti-idiotypic antibody to the bispecific antibody, and (iii) administering a drug or prodrug, capable of being converted to a more active drug by the tumor localized complex for therapeutic benefit in human

tumor patients, wherein the non-covalently bound complex is injected intravenously, the haptens are attached via a single reaction site to the enzyme and the bispecific antibody binds to both its antigen target and to its hapten target with a dissociation constant of at least 10^{-7}, more preferably at least 10^{-9}.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to have produced method of treating tumor cells in a patient comprising administering in sequence (i) a non-covalently bound complex comprising a bispecific antibody comprising at least one tumor-binding site and one hapten-binding site, and a hapten-enzyme covalent conjugate wherein the bispecific antibody and hapten-enzyme conjugate are mixed prior to administration in a ratio of 2:1, (ii) optionally administering a clearing agent that is an anti-idiotypic antibody to the bispecific antibody, and (iii) administering a drug or prodrug, capable of being converted to a more active drug by the tumor localized complex for therapeutic benefit in human tumor patients, wherein the non-covalently bound complex is injected intravenously, the haptens are attached via a single reaction site to the enzyme and the bispecific antibody binds to both its antigen target and to its hapten target with a dissociation constant of at least 10^{-7}, more preferably at least 10^{-9} in view of Hansen et al [a] and Gautherot et al and Barbet et al and Haisma et al because Hansen et al [a] teach a method of treating a patient comprising administering a bi-specific antibody or fragment comprising at least one arm that binds a tumor-associated antigen and at least one other arm that binds a hapten and a hapten-enzyme covalent conjugate comprising at least one hapten, wherein the hapten-enzyme conjugate is mixed with the bispecific antibody prior to administration (i.e., non-covalently bound complex), optionally administering a clearing agent that is an anti-idiotypic antibody to clear unbound non-covalent complexes and administering a chemotherapeutic drug or prodrug that is converted to a more active drug by the pre-targeted enzyme and Gautherot et al teach bispecific antibody-targeted bivalent haptens wherein saturation of the bispecific antibody occurred at a 2:1 ratio of bispecific antibody to bivalent hapten (i.e., 1 mol to 0.5 mol) and Barbet et al teach multivalent, multispecific antibodies or antigen-binding fragments thereof comprising two or more

binding sites, wherein at least one binding site has affinity towards a hapten moiety including HSG and at least one binding site has high affinity towards a tumor-associated antigen and a carrier molecule (affinity enhancement probe) comprising a therapeutic agent and at least two hapten moieties wherein the tumor-associated antigen binding site has a dissociation constant smaller than 10^{-8}M and the hapten binding site has a dissociation constant between 10^{-9}-10^{-7} and is administered by intravenous injection and Haisma et al teach that chemical conjugation of enzymes in antibody-directed enzyme prodrug therapy results in conjugate heterogeneity due to the lack of specificity of the reagents used for conjugation and necessitates additional purification steps and often results in reduced enzymatic activity or diminished binding activity of the conjugate, whereas recombinantly produced conjugates consist of a uniform product with predictable properties. Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to optimize the pre-targeting method of Hansen et al [a] by mixing the bispecific antibody and hapten-enzyme conjugate prior to administration in a ratio of 2:1 to saturate the bispecific antibody and produce a high affinity bispecific antibody wherein both the tumor-associated antigen and hapten binding sites have a dissociation constant smaller than 10^{-8}M and conjugate the haptens to the enzyme via a single reaction site to produce more uniform enzyme-hapten conjugates with predictable properties avoiding the requirement for further purification steps and reduced enzyme activity associated with conjugate heterogeneity and administer the non-covalent complex by intravenous injection in the pre-targeting method of Hansen et al [a]. Thus, there would be advantages to saturate the bispecific antibody with the hapten-enzyme conjugate, and use a high affinity bispecific antibody and uniform and predictable enzyme-hapten conjugates in the method of Hansen et al [a] for tumor therapy in patients. Thus, it would have been *prima facie* obvious to one skilled in the art at the time the invention was made to have produced method of treating tumor cells in a patient comprising administering in sequence (i) a non-covalently bound complex comprising a bispecific antibody comprising at least one tumor-binding site and one hapten-binding site, and a hapten-enzyme covalent conjugate wherein the bispecific antibody and hapten-enzyme conjugate are mixed prior

to administration in a ratio of 2:1, (ii) optionally administering a clearing agent that is an anti-idiotypic antibody to the bispecific antibody, and (iii) administering a drug or prodrug, capable of being converted to a more active drug by the tumor localized complex for therapeutic benefit in human tumor patients, wherein the non-covalently bound complex is injected intravenously, the haptens are attached via a single reaction site to the enzyme and the bispecific antibody binds to both its antigen target and to its hapten target with a dissociation constant of at least 10^{-7}, more preferably at least 10^{-9} in view of Hansen et al [a] and Gautherot et al and Barbet et al and Haisma et al.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

23. Claims 1-3, 5, 9-13, 15-22, 24-32, 34-35 and 42-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hansen et al [a] (WO 99/66951, 12/29/1999, cited on PTO-892 mailed 6/2/2006) in view of Gautherot et al (The Journal of Nuclear Medicine, 39(11):1937-1943, November 1998) and Danks et al (Clinical Cancer research 5:917-924, April 1999, cited on PTO-892 mailed 6/2/2006) and Searle P. F. (WO 00/43541, published 7/27/2000, cited on PTO-892 mailed 6/2/2006).

Claims 1-3, 5, 9-13, 15-16, 24-32, 34-35 and 42-43 and their interpretation have been described supra.

Claims 17-22 are being interpreted as being drawn to a method of treating target cells in a subject comprising administering in sequence a non-covalently bound complex to said human patient thereby forming a target-tissue localized complex, wherein said non-covalently bound complex comprises a multispecific targeting protein comprising at least one target-binding site and one hapten-binding site, and a hapten-enzyme covalent conjugate, optionally administering a clearing agent, and administering a chemotherapeutic drug or prodrug, capable of being converted to a more active drug by the target-tissue localized complex, wherein the enzyme is rat or human carboxylesterase or the enzyme is produced by recombinant techniques in bacteria and is modified by site-directed mutagenesis to enhance its catalytic rate.

Hansen et al [a] have been described supra. Hansen et al [a] do not specifically teach wherein the bispecific antibody and the hapten-enzyme conjugate are mixed prior to administration in a ratio from 5:1 to 1:5 or wherein the enzyme is rat or human carboxylesterase or the enzyme is produced by recombinant techniques in bacteria and is modified by site-directed mutagenesis to enhance its catalytic rate. These deficiencies are made up for in the teachings of Gautherot et al and Dansk et al and Searle.

Gautherot et al have been described supra.

Danks et al teach rabbit and human carboxylesterases for use in antibody-directed enzyme prodrug therapy of tumor cells, wherein tumor regression occurs in mice bearing xenografts that express rabbit or human carboxylesterases, particularly rabbit carboxylesterase upon administration of CPT-11 (see entire document, particularly pp. 922-923, Figs 1 and 5).

Searle teach recombinant methods in bacteria for enhancing the catalytic efficiency of prodrug activating enzymes, including site-directed mutagenesis (see entire document, particularly pp. 2, 4-9, 11).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced method of treating tumor cells in a patient comprising administering in sequence (i) a non-covalently bound complex comprising a bispecific antibody comprising at least one tumor-binding site and one hapten-binding site, and a hapten-enzyme covalent conjugate wherein the bispecific antibody and hapten-enzyme conjugate are mixed prior to administration in a ratio of 2:1, (ii) optionally administering a clearing agent that is an anti-idiotypic antibody to the bispecific antibody, and (iii) administering a prodrug, capable of being converted to a more active drug by the tumor localized complex for therapeutic benefit in human tumor patients, wherein the enzyme is rat or human carboxylesterase or the enzyme is produced by recombinant techniques in bacteria and is modified by site-directed mutagenesis to enhance its catalytic rate.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to have

produced method of treating tumor cells in a patient comprising administering in sequence (i) a non-covalently bound complex comprising a bispecific antibody comprising at least one tumor-binding site and one hapten-binding site, and a hapten-enzyme covalent conjugate wherein the bispecific antibody and hapten-enzyme conjugate are mixed prior to administration in a ratio of 2:1, (ii) optionally administering a clearing agent that is an anti-idiotypic antibody to the bispecific antibody, and (iii) administering a prodrug, capable of being converted to a more active drug by the tumor localized complex for therapeutic benefit in human tumor patients, wherein the enzyme is rat or human carboxylesterase or the enzyme is produced by recombinant techniques in bacteria and is modified by site-directed mutagenesis to enhance its catalytic rate in view of Hansen et al [a] and Gautherot et al and Danks et al and Searle because Hansen et al [a] teach a method of treating tumor cells in a patient comprising administering a bispecific antibody or fragment comprising at least one arm that binds a tumor associated antigen and at least one other arm that binds a hapten and a hapten-enzyme covalent conjugate comprising at least one hapten, wherein the hapten-enzyme conjugate is mixed with the bispecific antibody prior to administration (i.e., non-covalently bound complex), optionally administering a clearing agent that is an anti-idiotypic antibody to clear unbound non-covalent complexes and administering a chemotherapeutic drug or prodrug that is converted to a more active drug by the pre-targeted enzyme and Gautherot et al teach bispecific antibody-targeted bivalent haptens wherein saturation of the bispecific antibody occurred at a 2:1 ratio of bispecific antibody to bivalent hapten (i.e., 1 mol to 0.5 mol) and Danks et al teach antibody-directed enzyme prodrug therapy of tumor cells using rabbit or human carboxylesterase, which effectively inhibit tumor growth upon administration of the prodrug CPT-11 and Searle teach recombinant methods including site-directed mutagenesis for enhancing the catalytic efficiency of prodrug activating enzymes. Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to mix the bispecific antibody and hapten-enzyme conjugate prior to administration in a ratio of 2:1 to saturate the bispecific antibody and use rabbit or human carboxylesterase in the hapten-enzyme conjugate of Hansen et al [a] or modify the enzyme of the hapten-

enzyme conjugate by site-directed mutagenesis to enhance its catalytic rate, thereby increasing the efficiency at which a prodrug is converted to the active drug at the tumor site in the method of Hansen et al [a]. Thus, it would have been *prima facie* obvious to one skilled in the art at the time the invention was made to have produced method of treating tumor cells in a patient comprising administering in sequence (i) a non-covalently bound complex comprising a bispecific antibody comprising at least one tumor-binding site and one hapten-binding site, and a hapten-enzyme covalent conjugate wherein the bispecific antibody and hapten-enzyme conjugate are mixed prior to administration in a ratio of 2:1, (ii) optionally administering a clearing agent that is an anti-idiotypic antibody to the bispecific antibody, and (iii) administering a prodrug, capable of being converted to a more active drug by the tumor localized complex for therapeutic benefit in human tumor patients, wherein the enzyme is rat or human carboxylesterase or the enzyme is produced by recombinant techniques in bacteria and is modified by site-directed mutagenesis to enhance its catalytic rate in view of Hansen et al [a] and Gautherot et al and Danks et al and Searle.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

It is noted that the following three rejections for obviousness under 35 U.S.C. 103(a) are essentially as set forth above with the exception that Hansen et al [b] (U.S. Patent 7,074,405, filed 6/22/1999, cited on PTO-892 mailed 6/2/2006) is used in place of Hansen et al [a] (WO 99/66951, 12/29/1999, cited on PTO-892 mailed 6/2/2006), where Hansen et al [b] and Hansen et al [a] are equivalents.

24. Claims 1-3, 5, 7-13, 15-16, 24-32, 34-35 and 42-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hansen et al [b] (U.S. Patent 7,074,405, filed 6/22/1999, cited on PTO-892 mailed 6/2/2006) in view of Gautherot et al (The Journal of Nuclear Medicine, 39(11):1937-1943, November 1998) and Basu et al (International Journal of Cancer, 62:472-479, 1995, cited on PTO-892 mailed 6/2/2006).

The applied reference (Hansen et al [b]) has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

The claims and their interpretation have been described supra (see item no. 21 above).

Hansen et al [b] teach a method of treating a patient comprising administering a bispecific antibody or fragment having at least one arm that binds a targeted tissue or a tumor-associated antigen and at least one other arm that binds a hapten and a hapten-enzyme covalent conjugate comprising at least one hapten, wherein the hapten-enzyme conjugate is mixed with the targeting bispecific antibody prior to administration (i.e., non-covalently bound complex), optionally administering a galactosylated anti-idiotypic antibody (clearing agent) to the bi-specific antibody of the non-covalent complex to clear non-localized non-covalent complexes and administering a chemotherapeutic drug or prodrug that is converted to a more active drug by the pre-targeted enzyme (i.e., target-tissue-localized complex) (see entire document, particularly col. 2-4, 6-8, col. 18, lines 22-29, 59-67, col. 23 and Examples 13-14 and 26). Hansen et al [b] also teach bispecific or multispecific antibodies and antigen-binding fragments thereof that are monovalent or divalent (col. 12), are murine, chimeric, humanized or human antibodies and the hapten-enzyme comprises at least one hapten selected from fluorescein,

DTPA, indium-DTPA, NOTA, DOTA, indium-DOTA and yttrium-DOTA wherein the haptens are linked by a peptide from 2-10 amino acid residues and the enzyme is a glucuronidase or a carboxylesterase, and "can be adopted for use with any enzyme-drug pair" (col. 18, lines 16-17) according to Hansen et al [b] (see col. 7-11, 14-16, 18-22). Further, Hansen et al [b] teach various prodrugs including epirubicin, topotecan, maytansinoids, calicheamicins and CPT-11, which is converted by carboxylesterase to the active drug SN-38 that remains in the vicinity of the tumor due to its poor solubility, i.e., the prodrug has a greater aqueous solubility than the active drug produced by the non-covalent complex (see pp. 18-19, 21-22). Hansen et al [b] do not specifically teach wherein the bispecific antibody binds EGP-1 or wherein the bispecific antibody and the hapten-enzyme conjugate are mixed prior to administration in a ratio from 5:1 to 1:5, or 2:1 to 1:2, or the ratio is 2:1. These deficiencies are made up for in the teachings of Gautherot et al and Basu et al.

Gautherot et al have been described supra.

Basu et al have been described supra.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced method of treating EGP-1 expressing tumor cells in human patients comprising administering in sequence (i) a non-covalently bound complex comprising a bispecific antibody comprising at least one EGP-1-binding site and at least one hapten-binding site, and a hapten-enzyme covalent conjugate wherein the bispecific antibody and hapten-enzyme conjugate are mixed prior to administration in a ratio of 2:1, (ii) optionally administering a clearing agent that is an anti-idiotypic antibody to the bispecific antibody, and (iii) administering a chemotherapeutic drug or prodrug, capable of being converted to a more active drug by the EGP-1 localized complex for therapeutic benefit in human tumor patients.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to have produced method of treating EGP-1 expressing tumor cells in human patients comprising administering in sequence (i) a non-covalently bound complex comprising a bispecific antibody comprising at least one EGP-1-binding site and at least one hapten-

binding site, and a hapten-enzyme covalent conjugate wherein the bispecific antibody and hapten-enzyme conjugate are mixed prior to administration in a ratio of 2:1, (ii) optionally administering a clearing agent that is an anti-idiotypic antibody or a galactosylated anti-idiotypic antibody to the bispecific antibody, and (iii) administering a chemotherapeutic drug or prodrug, capable of being converted to a more active drug by the EGP-1 localized complex for therapeutic benefit in human tumor patients in view of Hansen et al [b] and Gautherot et al and Basu et al because Hansen et al [b] teach a method of treating a patient comprising administering a bi-specific antibody or fragment thereof comprising at least one arm that binds a tumor-associated antigen and at least one other arm that binds a hapten and a hapten-enzyme covalent conjugate comprising at least one hapten, wherein the hapten-enzyme conjugate is mixed with the targeting bi-specific antibody prior to administration (i.e., non-covalently bound complex), optionally administering an anti-idiotypic antibody or a galactosylated anti-idiotypic antibody (i.e., clearing agent) to said bispecific antibody to clear unbound non-covalent complexes and administering a chemotherapeutic prodrug that is converted to a more active drug by the pre-targeted enzyme and Gautherot et al teach bispecific antibody-targeted bivalent haptens wherein saturation of the bispecific antibody occurred at a 2:1 ratio of bispecific antibody to bivalent hapten (i.e., 1 mol to 0.5 mol) and Basu et al teach the EGP-1 antigen expressed in various human tumors of epithelial origin including breast, bladder, lung, ovary, prostate, pancreas and stomach as well as a monoclonal antibody to the EGP-1 antigen. Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to optimize the pre-targeting method of Hansen et al [b] by mixing the bispecific antibody and hapten-enzyme conjugate prior to administration in a ratio of 2:1 to saturate the bispecific antibody and target the human pancarcinoma antigen, EGP-1, for therapeutic benefit in a variety of human tumor patients, and the targetable conjugate (i.e., hapten-enzyme) of Hansen et al [b] provides flexibility in the therapeutic agent without the need for raising new bi-specific antibodies (see col. 2, lines 38-48). Thus, there would be an advantage to using the method of Hansen et al [b] in targeting the EGP-1 antigen that is expressed in numerous human tumors, including breast, bladder, lung, ovary, prostate, pancreas

and stomach and one of ordinary skill in the art would have a reasonable expectation of success in view of the teachings of Basu et al providing evidence that an EGP-1 antibody targets several carcinoma types in patients. Thus, it would have been *prima facie* obvious to one skilled in the art at the time the invention was made to have produced method of treating EGP-1 expressing tumor cells in human patients comprising administering in sequence (i) a non-covalently bound complex comprising a bispecific antibody comprising at least one EGP-1-binding site and at least one hapten-binding site, and a hapten-enzyme covalent conjugate wherein the bispecific antibody and hapten-enzyme conjugate are mixed prior to administration in a ratio of 2:1, (ii) optionally administering a clearing agent that is an anti-idiotypic antibody to the bispecific antibody, and (iii) administering a chemotherapeutic drug or prodrug, capable of being converted to a more active drug by the EGP-1 localized complex for therapeutic benefit in human tumor patients in view of Hansen et al [b] and Gautherot et al and Basu et al.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

25. Claims 1-3, 5-7, 9-16, 23-32, 34-35 and 42-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hansen et al [b] (U.S. Patent 7,074,405, filed 6/22/1999, cited on PTO-892 mailed 6/2/2006) in view of Gautherot et al (The Journal of Nuclear Medicine, 39(11):1937-1943, November 1998) and Barbet et al (U.S. Patent 5,256,395, issued 10/26/1993, cited on PTO-892 mailed 6/2/2006) and Haisma et al (Blood, 92(1):184-190, 1998, cited on PTO-892 mailed 6/2/2006).

Claims 1-3, 5, 7, 9, 11-13, 15-16, 24-32, 34-35 and 42-43 and their interpretation have been described supra (see item no. 22 above).

Claims 6, 10, 14 and 23 are being interpreted as being drawn to a method of treating target cells in a subject comprising administering in sequence a non-covalently bound complex to said human patient thereby forming a target-tissue localized complex, wherein said non-covalently bound complex comprises a multispecific targeting protein

comprising at least one target-binding site and one hapten-binding site (i.e., HSG), and a hapten-enzyme covalent conjugate, optionally administering a clearing agent, and administering a chemotherapeutic drug or prodrug, capable of being converted to a more active drug by the target-tissue localized complex, and wherein the multispecific targeting protein and the hapten-enzyme conjugate are in the ratios of from 5:1 to 1:5 and wherein the non-covalently bound complex is injected intravenously, and the haptens are attached via a single reaction site to the enzyme and the bi-specific targeting protein binds to both its antigen target and to its hapten target with a dissociation constant of at least 10^{-7}, more preferably at least 10^{-9}.

Hansen et al.[b] have been described supra. Hansen et al [b] do not specifically teach wherein the bispecific targeting protein and the hapten-enzyme conjugate are mixed prior to administration in a ratio from 5:1 to 1:5 or wherein the non-covalently bound complex is injected intravenously, the haptens (i.e., HSG) are attached via a single reaction site to the enzyme and the bispecific antibody binds to both its antigen target and to its hapten target with a dissociation constant of at least 10^{-7}, more preferably at least 10^{-9}. These deficiencies are made up for in the teachings of Gautherot et al and Barbet et al and Haisma et al.

Gautherot et al have been described supra.

Barbet et al have been described supra.

Haisma et al have been described supra.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced method of treating tumor cells in a patient comprising administering in sequence (i) a non-covalently bound complex comprising a bispecific antibody comprising at least one tumor-binding site and one hapten-binding site, and a hapten-enzyme covalent conjugate wherein the bispecific antibody and hapten-enzyme conjugate are mixed prior to administration in a ratio of 2:1, (ii) optionally administering a clearing agent that is an anti-idiotypic antibody to the bispecific antibody, and (iii) administering a drug or prodrug, capable of being converted to a more active drug by the tumor localized complex for therapeutic benefit in human tumor patients, wherein the non-covalently bound complex is injected intravenously, the

haptens are attached via a single reaction site to the enzyme and the bispecific antibody binds to both its antigen target and to its hapten target with a dissociation constant of at least 10^{-7}, more preferably at least 10^{-9}.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to have produced method of treating tumor cells in a patient comprising administering in sequence (i) a non-covalently bound complex comprising a bispecific antibody comprising at least one tumor-binding site and one hapten-binding site, and a hapten-enzyme covalent conjugate wherein the bispecific antibody and hapten-enzyme conjugate are mixed prior to administration in a ratio of 2:1, (ii) optionally administering a clearing agent that is an anti-idiotypic antibody to the bispecific antibody, and (iii) administering a drug or prodrug, capable of being converted to a more active drug by the tumor localized complex for therapeutic benefit in human tumor patients, wherein the non-covalently bound complex is injected intravenously, the haptens are attached via a single reaction site to the enzyme and the bispecific antibody binds to both its antigen target and to its hapten target with a dissociation constant of at least 10^{-7}, more preferably at least 10^{-9} in view of Hansen et al [b] and Gautherot et al and Barbet et al and Haisma et al because Hansen et al [b] teach a method of treating a patient comprising administering a bi-specific antibody or fragment comprising at least one arm that binds a tumor-associated antigen and at least one other arm that binds a hapten and a hapten-enzyme covalent conjugate comprising at least one hapten, wherein the hapten-enzyme conjugate is mixed with the bispecific antibody prior to administration (i.e., non-covalently bound complex), optionally administering a clearing agent that is an anti-idiotypic antibody to clear unbound non-covalent complexes and administering a chemotherapeutic drug or prodrug that is converted to a more active drug by the pre-targeted enzyme and Gautherot et al teach bispecific antibody-targeted bivalent haptens wherein saturation of the bispecific antibody occurred at a 2:1 ratio of bispecific antibody to bivalent hapten (i.e., 1 mol to 0.5 mol) and Barbet et al teach multivalent, multispecific antibodies or antigen-binding fragments thereof comprising two or more binding sites, wherein at least one binding site has affinity towards a hapten moiety

including HSG and at least one binding site has high affinity towards a tumor-associated antigen and a carrier molecule (affinity enhancement probe) comprising a therapeutic agent and at least two hapten moieties wherein the tumor-associated antigen binding site has a dissociation constant smaller than 10^{-8}M and the hapten binding site has a dissociation constant between 10^{-9}-10^{-7} and is administered by intravenous injection and Haisma et al teach that chemical conjugation of enzymes in antibody-directed enzyme prodrug therapy results in conjugate heterogeneity due to the lack of specificity of the reagents used for conjugation and necessitates additional purification steps and often results in reduced enzymatic activity or diminished binding activity of the conjugate, whereas recombinantly produced conjugates consist of a uniform product with predictable properties. Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to optimize the pre-targeting method of Hansen et al [a] by mixing the bispecific antibody and hapten-enzyme conjugate prior to administration in a ratio of 2:1 to saturate the bispecific antibody and produce a high affinity bispecific antibody wherein both the tumor-associated antigen and hapten binding sites have a dissociation constant smaller than 10^{-8}M and conjugate the haptens to the enzyme via a single reaction site to produce more uniform enzyme-hapten conjugates with predictable properties avoiding the requirement for further purification steps and reduced enzyme activity associated with conjugate heterogeneity and administer the non-covalent complex by intravenous injection in the pre-targeting method of Hansen et al [b]. Thus, there would be advantages to saturate the bispecific antibody with the hapten-enzyme conjugate, and use a high affinity bispecific antibody and uniform and predictable enzyme-hapten conjugates in the method of Hansen et al [b] for tumor therapy in patients. Thus, it would have been *prima facie* obvious to one skilled in the art at the time the invention was made to have produced method of treating tumor cells in a patient comprising administering in sequence (i) a non-covalently bound complex comprising a bispecific antibody comprising at least one tumor-binding site and one hapten-binding site, and a hapten-enzyme covalent conjugate wherein the bispecific antibody and hapten-enzyme conjugate are mixed prior to administration in a ratio of 2:1, (ii) optionally administering a clearing agent that is an

anti-idiotypic antibody to the bispecific antibody, and (iii) administering a drug or prodrug, capable of being converted to a more active drug by the tumor localized complex for therapeutic benefit in human tumor patients, wherein the non-covalently bound complex is injected intravenously, the haptens are attached via a single reaction site to the enzyme and the bispecific antibody binds to both its antigen target and to its hapten target with a dissociation constant of at least 10^{-7}, more preferably at least 10^{-9} in view of Hansen et al [b] and Gautherot et al and Barbet et al and Haisma et al.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

26. Claims 1-3, 5, 9-13, 15-22, 24-32, 34-35 and 42-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hansen et al [b] (U.S. Patent 7,074,405, filed 6/22/1999, cited on PTO-892 mailed 6/2/2006) in view of Gautherot et al (The Journal of Nuclear Medicine, 39(11):1937-1943, November 1998) and Danks et al (Clinical Cancer research 5:917-924, April 1999, cited on PTO-892 mailed 6/2/2006) and Searle P. F. (WO 00/43541, published 7/27/2000, cited on PTO-892 mailed 6/2/2006).

Claims 1-3, 5, 9-13, 15-16, 24-32, 34-35 and 42-43 and their interpretation have been described supra (see item no. 23 above).

Claims 17-22 are being interpreted as being drawn to a method of treating target cells in a subject comprising administering in sequence a non-covalently bound complex to said human patient thereby forming a target-tissue localized complex, wherein said non-covalently bound complex comprises a multispecific targeting protein comprising at least one target-binding site and one hapten-binding site, and a hapten-enzyme covalent conjugate, optionally administering a clearing agent, and administering a chemotherapeutic drug or prodrug, capable of being converted to a more active drug by the target-tissue localized complex, wherein the enzyme is rat or human carboxylesterase or the enzyme is produced by recombinant techniques in bacteria and is modified by site-directed mutagenesis to enhance its catalytic rate.

Hansen et al [b] have been described supra. Hansen et al [b] do not specifically teach wherein the bispecific antibody and the hapten-enzyme conjugate are mixed prior to administration in a ratio from 5:1 to 1:5 or wherein the enzyme is rat or human carboxylesterase or the enzyme is produced by recombinant techniques in bacteria and is modified by site-directed mutagenesis to enhance its catalytic rate. These deficiencies are made up for in the teachings of Gautherot et al and Dansk et al and Searle.

Gautherot et al have been described supra.

Danks et al have been described supra.

Searle P. F. has been described supra.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced method of treating tumor cells in a patient comprising administering in sequence (i) a non-covalently bound complex comprising a bispecific antibody comprising at least one tumor-binding site and one hapten-binding site, and a hapten-enzyme covalent conjugate wherein the bispecific antibody and hapten-enzyme conjugate are mixed prior to administration in a ratio of 2:1, (ii) optionally administering a clearing agent that is an anti-idiotypic antibody to the bispecific antibody, and (iii) administering a prodrug, capable of being converted to a more active drug by the tumor localized complex for therapeutic benefit in human tumor patients, wherein the enzyme is rat or human carboxylesterase or the enzyme is produced by recombinant techniques in bacteria and is modified by site-directed mutagenesis to enhance its catalytic rate.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to have produced method of treating tumor cells in a patient comprising administering in sequence (i) a non-covalently bound complex comprising a bispecific antibody comprising at least one tumor-binding site and one hapten-binding site, and a hapten-enzyme covalent conjugate wherein the bispecific antibody and hapten-enzyme conjugate are mixed prior to administration in a ratio of 2:1, (ii) optionally administering a clearing agent that is an anti-idiotypic antibody to the bispecific antibody, and (iii)

administering a prodrug, capable of being converted to a more active drug by the tumor localized complex for therapeutic benefit in human tumor patients, wherein the enzyme is rat or human carboxylesterase or the enzyme is produced by recombinant techniques in bacteria and is modified by site-directed mutagenesis to enhance its catalytic rate in view of Hansen et al [b] and Gautherot et al and Danks et al and Searle because Hansen et al [b] teach a method of treating tumor cells in a patient comprising administering a bispecific antibody or fragment comprising at least one arm that binds a tumor associated antigen and at least one other arm that binds a hapten and a hapten-enzyme covalent conjugate comprising at least one hapten, wherein the hapten-enzyme conjugate is mixed with the bispecific antibody prior to administration (i.e., non-covalently bound complex), optionally administering a clearing agent that is an anti-idiotypic antibody to clear unbound non-covalent complexes and administering a chemotherapeutic drug or prodrug that is converted to a more active drug by the pre-targeted enzyme and Gautherot et al teach bispecific antibody-targeted bivalent haptens wherein saturation of the bispecific antibody occurred at a 2:1 ratio of bispecific antibody to bivalent hapten (i.e., 1 mol to 0.5 mol) and Danks et al teach antibody-directed enzyme prodrug therapy of tumor cells using rabbit or human carboxylesterase, which effectively inhibit tumor growth upon administration of the prodrug CPT-11 and Searle teach recombinant methods including site-directed mutagenesis for enhancing the catalytic efficiency of prodrug activating enzymes. Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to mix the bispecific antibody and hapten-enzyme conjugate prior to administration in a ratio of 2:1 to saturate the bispecific antibody and use rabbit or human carboxylesterase in the hapten-enzyme conjugate of Hansen et al [b] or modify the enzyme of the hapten-enzyme conjugate by site-directed mutagenesis to enhance its catalytic rate, thereby increasing the efficiency at which a prodrug is converted to the active drug at the tumor site in the method of Hansen et al [b]. Thus, it would have been *prima facie* obvious to one skilled in the art at the time the invention was made to have produced method of treating tumor cells in a patient comprising administering in sequence (i) a non-covalently bound complex comprising a bispecific antibody comprising at least one

tumor-binding site and one hapten-binding site, and a hapten-enzyme covalent conjugate wherein the bispecific antibody and hapten-enzyme conjugate are mixed prior to administration in a ratio of 2:1, (ii) optionally administering a clearing agent that is an anti-idiotypic antibody to the bispecific antibody, and (iii) administering a prodrug, capable of being converted to a more active drug by the tumor localized complex for therapeutic benefit in human tumor patients, wherein the enzyme is rat or human carboxylesterase or the enzyme is produced by recombinant techniques in bacteria and is modified by site-directed mutagenesis to enhance its catalytic rate in view of Hansen et al [b] and Gautherot et al and Danks et al and Searle.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

27. Claims 1-3, 5-32, 34-35 and 42-43 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 16 and 18 of U.S. Patent No. 6,962,702 B2 in view of Hansen et al [a] (WO 99/66951, 12/29/1999, cited on PTO-892 mailed 6/2/2006) and Gautherot et al (The Journal of Nuclear Medicine, 39(11):1937-1943, November 1998) and Basu et al (International Journal of Cancer, 62:472-479, 1995, cited on PTO-892 mailed 6/2/2006) and Barbet et al (U.S. Patent 5,256,395, issued 10/26/1993, cited on PTO-892 mailed 6/2/2006) and Haisma et al (Blood, 92(1):184-190, 1998, cited on PTO-892 mailed 6/2/2006) and Danks et al (Clinical Cancer research 5:917-924, April 1999, cited on PTO-892 mailed 6/2/2006) and Searle (WO 00/43541, published 7/27/2000, cited on PTO-892 mailed 6/2/2006).

The instant claims are drawn to a method of treating target cells in a mammalian or human subject comprising administering in sequence a non-covalently bound complex to said mammalian or human subject thereby forming a target-tissue localized complex, wherein said non-covalently bound complex comprises a multispecific targeting protein comprising at least one target-binding site and one hapten-binding site, and a hapten-enzyme covalent conjugate, wherein said at least one target- binding site binds to the target cells/tissue and wherein said hapten-binding site in non-covalently

bound to the hapten-enzyme covalent conjugate, optionally administering a clearing agent, and administering a chemotherapeutic drug or prodrug, capable of being converted to a more active drug by the target-tissue localized complex and the chemotherapeutic prodrug has greater solubility than the active drug produced by the non-covalently bound complex and the prodrug is a prodrug of a camptothecin, doxorubicin, taxol, actinomycin, maytansine, calicheamicin or epithilone class of drug or is the prodrug CPT-11, a prodrug of SN-38. Further, the multispecific targeting protein is a mutlispecific antibody or multispecific antibody fragment, is at least bi-specific, multivalent, is murine, chimeric, humanized or human and binds EGP-1 and the multispecific antibody binds both its antigen and the hapten with a dissociation constant of at least 10^{-7}, more preferably at least 10^{-9}, is administered by intravenous injection and the hapten-enzyme comprises at least one hapten, selected from HSG, DTPA, indium-DTPA, DOTA, indium-DOTA, yttrium-DOTA, fluorescein or biotin and the haptens are linked to the enzyme via a single reaction site by a peptide from 2-10, 2-5 or 3 amino acid residues in length and the enzyme of the hapten-enzyme conjugate is an esterase, amidase, glucuronidase, galactosidase or carboxylesterase, is recombinantly produced in yeast, bacteria, plants, insect cells or animals and is modified by site-directed mutagenesis to increase the rate of enzyme-substrate catalysis and the clearing agent is an anti-idiotypic antibody or a galactosylated anti-idiotypic antibody to the multispecific targeting protein and wherein the multispecific targeting protein and the hapten-enzyme conjugate are mixed prior to administration in a ratio from 5:1 to 1:5, or 2:1 to 1:2, or the ratio is 2:1.

Claims 1, 16, and 18 of U.S. Patent No. 6,962,702 B2 are drawn to a method of treating diseased tissues in a subject comprising administering a bi-specific antibody or antibody fragment having at least one arm that specifically binds a targeted tissue and at least one arm that binds a targetable conjugate comprising at least two HSG haptens (i.e., comprises the Fv of monoclonal antibody 679), optionally administering a clearing composition to clear non-localized antibody or antibody fragments from circulation, administering to said subject a targetable conjugate that comprises at least two HSG haptens and a diagnostic or therapeutic agent or enzyme and when said targetable

conjugate comprises an enzyme, further administering to said subject a prodrug capable of being converted to a drug at the target site, wherein said at least one arm that specifically binds a targeted tissue is a monoclonal antibody or a fragment of a monoclonal antibody and the targeted tissue is a tumor. Claims 1, 16 and 18 of U.S. Patent No. 6,962,702 B2 do not specifically teach wherein the bispecific antibody is mixed with the hapten-enzyme conjugate prior to administration in a ratio from 5:1 to 1:5, or 2:1 to 1:2, or 2:1 to form a non-covalently bound complex optionally followed by administration of a galactosylated anti-idiotypic antibody (clearing agent) to the bi-specific antibody or antibody fragment or wherein the bi-specific antibody is multivalent, murine, chimeric, humanized, or human, is injected in intravenously, binds EGP-1 and wherein the haptens of the hapten-enzyme conjugate are attached via a single reaction site to the enzyme or are linked by a peptide from about 2-10, 2-5 or 3 amino acid residues in length and wherein the enzyme is an esterase, amidase, glucuronidase, galactosidase or is a carboxylesterase selected from rat, mouse rabbit, porcine or human carboxylesterase, or the enzyme is produced by recombinant techniques in yeast, bacteria, plants, insect cells or animals and is modified by site-directed mutagenesis to increase the rate of catalysis and wherein the bi-specific antibody binds both the target tissue and the hapten with a dissociation constant of at least 10^{-7}, more preferably at least 10^{-9} and wherein the prodrug is a prodrug of camptothecin, doxorubicin, taxol, actinomycin, maytansine, calicheamicin or epithilone class of drug or is the prodrug CPT-11 (i.e., the prodrug of SN-38) or wherein the subject is a human. These deficiencies are made up for in the teachings of Hansen et al [a] and Gautherot et al and Basu et al and Barbet et al and Haisma et al and Danks et al and Searle.

Hansen et al [a] have been described supra.

Gautherot et al have been described supra.

Basu et al have been described supra.

Barbet et al have been described supra.

Haisma et al have been described supra.

Danks et al have been described supra.

Searle has been described supra.

The claims in the instant application are obvious variants of claims 1, 16, and 18 of U.S. Patent No. 6,962,702 B2 because it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the method of claims 1, 16 and 18 of U.S. Patent No. 6,962,702 B2 wherein the targeting bi-specific antibody is mixed with the hapten-enzyme conjugate in a ratio of 2:1 prior to administration to form a non-covalently bound complex, optionally followed by administration of a galactosylated anti-idiotypic antibody (clearing agent) to the bispecific antibody or antibody fragment and wherein the bispecific antibody is multivalent, murine, chimeric, humanized, or human, is injected intravenously, binds the tumor-associated antigen EGP-1, has a dissociation constant of at least 10^{-7}, more preferably at least 10^{-9} for both the antigenic target and the hapten, and wherein the haptens of the hapten-enzyme conjugate are attached via a single reaction site to the enzyme or are linked by a peptide from about 2-10, 2-5 or 3 amino acid residues in length and wherein the enzyme is an esterase, amidase, glucuronidase, galactosidase or is a carboxylesterase selected from rat, mouse rabbit, porcine or human carboxylesterase, or the enzyme is produced by recombinant techniques in yeast, bacteria, plants, insect cells or animals and is modified by site-directed mutagenesis to increase the rate of catalysis and wherein the prodrug is a prodrug of camptothecin, doxorubicin, taxol, actinomycin, maytansine, calicheamicin or epithilone class of drug or is the prodrug CPT-11 (i.e., the prodrug of SN-38) and the subject is a human.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to modify the method of claims 1, 16 and 18 of U.S. Patent No. 6,962,702 B2 wherein the targeting bispecific antibody is mixed with the hapten-enzyme conjugate in a ratio of 2:1 prior to administration to form a non-covalently bound complex, optionally followed by administration of a galactosylated anti-idiotypic antibody (clearing agent) to the bispecific antibody or antibody fragment and wherein the bispecific antibody is multivalent, murine, chimeric, humanized, or human, is injected intravenously, binds the tumor-associated antigen EGP-1, has a dissociation constant of at least 10^{-7}, more preferably at least 10^{-9} for both the antigenic target and the hapten, and wherein the

haptens of the hapten-enzyme conjugate are attached via a single reaction site to the enzyme or are linked by a peptide from about 2-10, 2-5 or 3 amino acid residues in length and wherein the enzyme is an esterase, amidase, glucuronidase, galactosidase or is a carboxylesterase selected from rat, mouse rabbit, porcine or human carboxylesterase, or the enzyme is produced by recombinant techniques in yeast, bacteria, plants, insect cells or animals and is modified by site-directed mutagenesis to increase the rate of catalysis and wherein the prodrug is a prodrug of camptothecin, doxorubicin, taxol, actinomycin, maytansine, calicheamicin or epithilone class of drug or is the prodrug CPT-11 (i.e., the prodrug of SN-38) and the subject is a human in view of Hansen et al [a] and Gautherot et al and Basu et al and Barbet et al and Haisma et al and Danks et al and Searle because Hansen et al [a] teach a method of treating a patient comprising administering a bispecific antibody or fragment having at least one arm that binds a tumor-associated antigen and at least one other arm that binds a hapten and a hapten-enzyme covalent conjugate comprising at least one hapten, wherein the hapten-enzyme conjugate is mixed with the targeting bispecific antibody prior to administration (i.e., non-covalently bound complex), optionally administering a galactosylated anti-idiotypic antibody to the bispecific antibody of the non-covalent complex to clear non-localized non-covalent complexes and administering a chemotherapeutic drug or prodrug that is converted to a more active drug by the pre-targeted enzyme and Hansen et al [a] also teach bi-specific or multispecific antibodies and antigen-binding fragments thereof that are monovalent or divalent and murine, chimeric, humanized and human antibodies and the hapten-enzyme comprises at least one hapten selected from fluorescein, DTPA, indium-DTPA, NOTA, DOTA, indium-DOTA and yttrium-DOTA wherein the haptens are linked by a peptide from 2-10 amino acid residues and the enzyme is a glucuronidase or a carboxylesterase, and various prodrugs including epirubicin, topotecan, maytansinoids, calicheamicins and CPT-11, which is converted by carboxylesterase to the active drug SN-38 that remains in the vicinity of the tumor due to its poor solubility, i.e., the prodrug has a greater aqueous solubility than the active drug produced by the non-covalent complex and Gautherot et al teach bispecific antibody-targeted bivalent haptens wherein saturation of the

bispecific antibody occurred at a 2:1 ratio of bispecific antibody to bivalent hapten (i.e., 1 mol to 0.5 mol) and Basu et al teach the epithelial glycoprotein-1 (EGP-1) expressed in various human tumors of epithelial origin including breast, bladder, lung, ovary, prostate, pancreas and stomach and Barbet et al teach intravenous injection of multivalent, multispecific antibodies or antigen-binding fragments thereof comprising two or more binding sites, wherein at least one binding site has affinity towards a hapten moiety (i.e., HSG) and at least one binding site has high affinity towards a tumor-associated antigen and a carrier molecule (affinity enhancement probe) comprising a therapeutic agent and at least two hapten moieties wherein the tumor-associated antigen binding site has a dissociation constant smaller than 10^{-8}M and the hapten binding site has a dissociation constant between 10^{-9}-10^{-7} and Haisma et al teach that chemical conjugation of enzymes in antibody-directed enzyme prodrug therapy results in conjugate heterogeneity due to the lack of specificity of the reagents used for conjugation and necessitates additional purification steps and often results in reduced enzymatic activity or diminished binding activity of the conjugate, whereas recombinantly produced conjugates consist of a uniform product with predictable properties and Danks et al teach antibody-directed enzyme prodrug therapy of tumor cells using rabbit or human carboxylesterase, which effectively inhibit tumor growth upon administration of the prodrug CPT-11 and Searle teach recombinant methods including site-directed mutagenesis for enhancing the catalytic efficiency of prodrug activating enzymes. Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the method of claims 1, 16 and 18 of U.S. Patent No. 6,962,702 B2 wherein the targeting bi-specific antibody is mixed with the hapten-enzyme conjugate in a ratio of 2:1 prior to administration to form a non-covalently bound complex, optionally followed by administration of a galactosylated anti-idiotypic antibody (clearing agent) to the bi-specific antibody or antibody fragment and wherein the bi-specific antibody is multivalent, murine, chimeric, humanized, or human, is injected intravenously, binds the tumor-associated antigen EGP-1, has a dissociation constant of at least 10^{-7}, more preferably at least 10^{-9} for both the antigenic target and the hapten, and wherein the haptens of the hapten-

enzyme conjugate are attached via a single reaction site to the enzyme or are linked by a peptide from about 2-10, 2-5 or 3 amino acid residues in length and wherein the enzyme is an esterase, amidase, glucuronidase, galactosidase or is a carboxylesterase selected from rat, mouse rabbit, porcine or human carboxylesterase, or the enzyme is produced by recombinant techniques in yeast, bacteria, plants, insect cells or animals and is modified by site-directed mutagenesis to increase the rate of catalysis and wherein the prodrug is a prodrug of camptothecin, doxorubicin, taxol, actinomycin, maytansine, calicheamicin or epithilone class of drug or is the prodrug CPT-11 (i.e., the prodrug of SN-38) and the subject is a human in view of claims 1, 16 and 18 of U.S. Patent No. 6,962,702 B2 and Hansen et al [a] and Gautherot et al and Basu et al and Barbet et al and Haisma et al and Danks et al and Searle.

28. Claims 1-3, 5-32, 34-35 and 42-43 are directed to an invention not patentably distinct from claims 1, 16 and 18 of commonly assigned U.S. Patent No. 6,962,702 B2. Specifically, see above.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP Chapter 2300). Commonly assigned U.S. Patent 6,962,702 B2, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications pending on or after December 10, 2004.

29. Claims 1-3, 5-32, 34-35 and 42-43 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-8 of U.S. Patent 7,074,405 in view of in view of Hansen et al [a] (WO 99/66951, 12/29/1999, cited on PTO-892 mailed 6/2/2006) and Gautherot et al (The Journal of Nuclear Medicine, 39(11):1937-1943, November 1998) and Basu et al (International Journal of Cancer, 62:472-479, 1995, cited on PTO-892 mailed 6/2/2006) and Barbet et al (U.S. Patent 5,256,395, issued 10/26/1993, cited on PTO-892 mailed 6/2/2006) and Haisma et al (Blood, 92(1):184-190, 1998, cited on PTO-892 mailed 6/2/2006) and Danks et al (Clinical Cancer research 5:917-924, April 1999, cited on PTO-892 mailed 6/2/2006) and Searle (WO 00/43541, published 7/27/2000, cited on PTO-892 mailed 6/2/2006).

Instant claims 1-3, 5-32, 34-35 and 42-43 have been described supra.

Claims 1-8 of U.S. Patent 7,074,405 recite a method of treating diseased tissues in a subject comprising administering a bispecific antibody or antibody fragment having at least one arm that specifically binds a targeted tissue and at least one arm that binds a targetable conjugate, optionally administering a clearing composition to clear non-localized antibody or antibody fragments from circulation, administering to said subject a targetable conjugate that comprises a carrier portion and one or more conjugated enzymes, said carrier portion bears at least one hapten recognized by at least one arm of the bi-specific antibody, and administering to said subject a drug or prodrug, wherein said bi-specific antibody is a monoclonal antibody or a fragment of a monoclonal antibody or is humanized and wherein the carrier portion comprises a carbohydrate. Claims 1-8 of U.S. Patent 7,074,405 do not specifically teach wherein the targeting bispecific antibody is mixed with the hapten-enzyme conjugate (i.e., targetable conjugate) in a ratio of 2:1 prior to administration to form a non-covalently bound complex optionally followed by administration of a galactosylated anti-idiotypic antibody (clearing agent) to the bi-specific antibody or antibody fragment or wherein the bi-specific antibody is multivalent, murine, chimeric, humanized, or human, is injected in intravenously, binds EGP-1 and wherein the haptens of the hapten-enzyme conjugate are attached via a single reaction site to the enzyme or are linked by a peptide from about 2-10, 2-5 or 3 amino acid residues in length and wherein the enzyme is an

esterase, amidase, glucuronidase, galactosidase or is a carboxylesterase selected from rat, mouse rabbit, porcine or human carboxylesterase, or the enzyme is produced by recombinant techniques in yeast, bacteria, plants, insect cells or animals and is modified by site-directed mutagenesis to increase the rate of catalysis and wherein the bi-specific antibody binds both the target tissue and the hapten with a dissociation constant of at least 10^{-7}, more preferably at least 10^{-9} and wherein the prodrug is a prodrug of camptothecin, doxorubicin, taxol, actinomycin, maytansine, calicheamicin or epithilone class of drug or is the prodrug CPT-11 (i.e., the prodrug of SN-38) or wherein the subject is a human. These deficiencies are made up for in the teachings of Hansen et al [a] and Gautherot et al and Basu et al and Barbet et al and Haisma et al and Danks et al and Searle.

Hansen et al [a] have been described supra.

Gautherot et al have been described supra.

Basu et al have been described supra.

Barbet et al have been described supra.

Haisma et al have been described supra.

Danks et al have been described supra.

Searle has been described supra.

The claims in the instant application are obvious variants of claims 1-8 of U.S. Patent 7,074,405 because it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the method of claims 1-8 of U.S. Patent 7,074,405 wherein the targeting bi-specific antibody is mixed with the hapten-enzyme conjugate in a ratio of 2:1 prior to administration to form a non-covalently bound complex optionally followed by administration of a galactosylated anti-idiotypic antibody (clearing agent) to the bi-specific antibody or antibody fragment and wherein the bi-specific antibody is multivalent, murine, chimeric, humanized, or human, is injected in intravenously, binds the tumor-associated antigen EGP-1, has a dissociation constant of at least 10^{-7}, more preferably at least 10^{-9} for both the antigenic target and the hapten, and wherein the haptens of the hapten-enzyme conjugate are attached via a single reaction site to the enzyme or are linked by a peptide from about

2-10, 2-5 or 3 amino acid residues in length and wherein the enzyme is an esterase, amidase, glucuronidase, galactosidase or is a carboxylesterase selected from rat, mouse rabbit, porcine or human carboxylesterase, or the enzyme is produced by recombinant techniques in yeast, bacteria, plants, insect cells or animals and is modified by site-directed mutagenesis to increase the rate of catalysis and wherein the prodrug is a prodrug of camptothecin, doxorubicin, taxol, actinomycin, maytansine, calicheamicin or epithilone class of drug or is the prodrug CPT-11 (i.e., the prodrug of SN-38) and the subject is a human.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to modify the method of claims 1-8 of U.S. Patent 7,074,405 wherein the targeting bispecific antibody is mixed with the hapten-enzyme conjugate in a ratio of 2:1 prior to administration to form a non-covalently bound complex optionally followed by administration of a galactosylated anti-idiotypic antibody (clearing agent) to the bispecific antibody or antibody fragment and wherein the bispecific antibody is multivalent, murine, chimeric, humanized, or human, is injected in intravenously, binds the tumor-associated antigen EGP-1, has a dissociation constant of at least 10^{-7}, more preferably at least 10^{-9} for both the antigenic target and the hapten, and wherein the haptens of the hapten-enzyme conjugate are attached via a single reaction site to the enzyme or are linked by a peptide from about 2-10, 2-5 or 3 amino acid residues in length and wherein the enzyme is an esterase, amidase, glucuronidase, galactosidase or is a carboxylesterase selected from rat, mouse rabbit, porcine or human carboxylesterase, or the enzyme is produced by recombinant techniques in yeast, bacteria, plants, insect cells or animals and is modified by site-directed mutagenesis to increase the rate of catalysis and wherein the prodrug is a prodrug of camptothecin, doxorubicin, taxol, actinomycin, maytansine, calicheamicin or epithilone class of drug or is the prodrug CPT-11 (i.e., the prodrug of SN-38) and the subject is a human in view of Hansen et al [a] and Gautherot et al and Basu et al and Barbet et al and Haisma et al and Danks et al and Searle because Hansen et al [a] teach a method of treating a patient comprising administering a bispecific antibody or fragment having at least one arm that binds a targeted tissue

and at least one other arm that binds a hapten and a hapten-enzyme covalent conjugate comprising at least one hapten, wherein the hapten-enzyme conjugate is mixed with the targeting bispecific antibody prior to administration (i.e., non-covalently bound complex), optionally administering a galactosylated anti-idiotypic antibody to the bi-specific antibody of the non-covalent complex to clear non-localized non-covalent complexes and administering a chemotherapeutic drug or prodrug that is converted to a more active drug by the pre-targeted enzyme and Hansen et al [a] also teach bispecific or multispecific antibodies and antigen-binding fragments thereof that are monovalent or divalent and murine, chimeric, humanized and human antibodies and the hapten-enzyme comprises at least one hapten selected from fluorescein, DTPA, indium-DTPA, NOTA, DOTA, indium-DOTA and yttrium-DOTA wherein the haptens are linked by a peptide from 2-10 amino acid residues and the enzyme is a glucuronidase or a carboxylesterase, and various prodrugs including epirubicin, topotecan, maytansinoids, calicheamicins and CPT-11, which is converted by carboxylesterase to the active drug SN-38 that remains in the vicinity of the tumor due to its poor solubility, i.e., the prodrug has a greater aqueous solubility than the active drug produced by the non-covalent complex and Gautherot et al teach bispecific antibody-targeted bivalent haptens wherein saturation of the bispecific antibody occurred at a 2:1 ratio of bispecific antibody to bivalent hapten (i.e., 1 mol to 0.5 mol) and Basu et al teach the epithelial glycoprotein-1 (EGP-1) expressed in various human tumors of epithelial origin including breast, bladder, lung, ovary, prostate, pancreas and stomach and Barbet et al teach intravenous injection of a multivalent, multispecific antibodies or antigen-binding fragments thereof comprising two or more binding sites, wherein at least one binding site has affinity towards a hapten moiety (i.e., HSG) and at least one binding site has high affinity towards a tumor-associated antigen and a carrier molecule (affinity enhancement probe) comprising a therapeutic agent and at least two hapten moieties wherein the tumor-associated antigen binding site has a dissociation constant smaller than 10^{-8}M and the hapten binding site has a dissociation constant between 10^{-9}-10^{-7} and Haisma et al teach that chemical conjugation of enzymes in antibody-directed enzyme prodrug therapy results in conjugate heterogeneity due to the lack of specificity

of the reagents used for conjugation and necessitates additional purification steps and often results in reduced enzymatic activity or diminished binding activity of the conjugate, whereas recombinantly produced conjugates consist of a uniform product with predictable properties and Danks et al teach antibody-directed enzyme prodrug therapy of tumor cells using rabbit or human carboxylesterase, which effectively inhibit tumor growth upon administration of the prodrug CPT-11 and Searle teach recombinant methods including site-directed mutagenesis for enhancing the catalytic efficiency of prodrug activating enzymes. Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the method of claims 1-8 of U.S. Patent 7,074,405 wherein the targeting bispecific antibody is mixed with the hapten-enzyme conjugate in a ratio of 2:1 prior to administration to form a non-covalently bound complex, optionally followed by administration of a galactosylated anti-idiotypic antibody (clearing agent) to the bispecific antibody or antibody fragment and wherein the bi-specific antibody is multivalent, murine, chimeric, humanized, or human, is injected in intravenously, binds the tumor-associated antigen EGP-1, has a dissociation constant of at least 10^{-7}, more preferably at least 10^{-9} for both the antigenic target and the hapten, and wherein the haptens of the hapten-enzyme conjugate are attached via a single reaction site to the enzyme or are linked by a peptide from about 2-10, 2-5 or 3 amino acid residues in length and wherein the enzyme is an esterase, amidase, glucuronidase, galactosidase or is a carboxylesterase selected from rat, mouse rabbit, porcine or human carboxylesterase, or the enzyme is produced by recombinant techniques in yeast, bacteria, plants, insect cells or animals and is modified by site-directed mutagenesis to increase the rate of catalysis and wherein the prodrug is a prodrug of camptothecin, doxorubicin, taxol, actinomycin, maytansine, calicheamicin or epithilone class of drug or is the prodrug CPT-11 (i.e., the prodrug of SN-38) and the subject is a human in view of claims 1-8 of U.S. Patent 7,074,405 and Hansen et al [a] and Gautherot et al and Basu et al and Barbet et al and Haisma et al and Danks et al and Searle.

30. Claims 1-3, 5-32, 34-35 and 42-43 are directed to an invention not patentably distinct from claims 1-8 of commonly assigned U.S. Patent 7,074,405. Specifically, see above.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP Chapter 2300). Commonly assigned U.S. Patent 7,074,405, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications pending on or after December 10, 2004.

Conclusion

31. No claim is allowed.

32. Applicant's amendment necessitated the new grounds of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

33. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 6:00 PM, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached at (571) 272-0832. The official fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,
David J. Blanchard
571-272-0827